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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,242	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/12/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7,12-14,23 and 46-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,12-14,23 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 8/12/2004, in which several claims were amended (claims 1-2, 4, 7, 12-13 and 23), claims were cancelled (claims 3, 5-6, 8-11, 15-22 and 24-45) and in which new claims were added (claims 46-48). It is noted that the proposed amendment of 4/21/2004 indicated that an additional new claim, claim 49, was submitted. This claim is not present in the response filed 8/12/2004. However, this is not an issue with regard to proper amendment practice since the amendment of 4/21/2004 was not entered (see the Notice of Non-Responsive Amendment mailed on 7/14/2004). Claims 1-2, 7, 12-14, 23 and 46-48 are pending in the instant application.

Any rejection of record in the previous office action mailed 10/21/2003 not addressed herein is withdrawn. As the new rejections made herein were necessitated by applicant's amendment of the claims in the response filed 8/12/2004, this action is FINAL.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The instant specification uses legal phraseology throughout (e.g. "said"). Appropriate correction is required.

Claim Objections

Claim 23 objected to because of the following informalities: the word "for" is directly repeated in line 2 of the claim. Also, the claim is grammatically clumsy in that no article (e.g. "the") appears prior to the word "aforementioned". Appropriate correction is required.

Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1, upon which claim 48 depends, already specifies that the peptide or protein encoded by the nucleic acid enables selective identification of the transformed cells. It is unclear how the terms "marker protein" or "marker peptide" further limit this limitation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-2, 7, 12-14, 23 and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by applicants' amendment of the claims in the response filed 8/12/2004.**

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "...the method comprising (i) bringing the substance into contact with the cell, wherein step (i) is the only prerequisite for the uptake of the substance by the cell..." are unclear. The cited phrase is unclear in that it is unclear what is encompassed by the term "prerequisite" in the context of the claimed method. The term "prerequisite" is not explicitly defined in the instant specification and it is not clear, for example, what steps and/or products are encompassed by the recited term in the context of the claimed method. For example, it is unclear as the claim is written whether culturing the progenitor or stem cell prior to contact is considered a "prerequisite" for practicing the claimed method. It would be remedial with regard to this grounds of rejection to explicitly indicate what steps and/or products are intended to be considered as excluded "prerequisites" for practicing the claimed method.

Claim 1 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the cells" as recited in line 4 of the claim.

Claim 23 is vague and indefinite in that the metes and bounds of the phrase "...said protein or detectable signal is used for [for] testing or screening of aforementioned protein or signal..." are unclear. While the cited phrase does recite a positive action step of "using" the protein or detectable signal, it does not provide an indication of what way or to what end the signal or protein is to be used. Consequently, it is impossible to determine what actual steps are encompassed by the cited phrase. It appears from reading the specification that the cited phrase may be intended to specify that the signal or protein be used to identify or sort progenitor or stem cells that have been transformed with the recited nucleic acid.

Claim 46 is vague and indefinite in that the metes and bounds of the phrase "...without the use of facilitating drugs, carriers, soluble receptors, chemicals or any special devices that facilitate uptake or transport of DNA..." are unclear. First, it is unclear as the claim is written whether the terms "facilitate" or "facilitating" refer to each of the recited products or only to "drugs" and "special devices". The claim is further indefinite in that it is unclear in what way or to what degree the recited products "facilitate" the uptake of DNA. This is compounded by the fact that the terms "carriers", "chemicals" or "special devices" are not explicitly defined in the instant specification. For example, is water considered as a chemical or carrier for the particular nucleic acid that aids in transformation of the target progenitor or stem cells? After all, the transformation experiment described in the working example appears to have been done with cells in culture and would necessarily have been done in an aqueous environment. Similarly, would the tissue culture flask comprising the cells be considered as a "special device" since it is used in the transformation experiment?

The following 112 2nd paragraph rejection is maintained for reasons of record in the office action mailed on 10/21/2003.

Claim 7 is vague and indefinite in that the metes and bounds of the words "specific cDNA" are unclear. In what sense is the recited cDNA "specific"? It would be remedial to amend the claim language to explicitly recite in what way the cDNA is "specific".

Response to Arguments/"specific cDNA"

Applicant's arguments filed 4/21/2004 have been fully considered but they are not persuasive. In the original response to the previous office action, filed on 4/21/2004, applicants'

have essentially argued that the term cDNA is specific in itself and that the skilled artisan would recognized what is intended by the term "cDNA". This response is not persuasive as it does not address the grounds of rejection made in the previous office action. In what sense is the recited cDNA specific? The fact that the term "specific" is used as an adjective to describe the word "cDNA" implies that there is some additional limitation conveyed by the term. For example, it appears that the term "specific" may be intended to indicate that the "specific" cDNA encodes the peptide or protein that enables selective identification of the transformed cells. Again, the concept of a "specific" cDNA is not defined in the specification and it remains unclear what structural/functional characteristics are encompassed by the term "specific cDNA".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 7, 12-14, 23 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/12/2004.**

Claim 1 has been amended to recite the limitation "...the method comprising (i) bringing the substance into contact with the cell, wherein step (i) is the only prerequisite for the uptake of the substance by the cell...". The response filed 4/21/2004 indicates that support for this

amendment of claim 1 is present in the originally filed claims and specification. However, upon review of the entire originally filed claims and specification, it does not appear that there is any literal or inherent support for the recited phrase. Therefore, the amended claims recite impermissible NEW MATTER.

Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/12/2004.**

Amended claim 47 now recites, "...wherein the cell has not been modified to facilitate uptake of DNA...". There does not appear to be literal support in the specification and claims as originally filed for this limitation. Applicants' response has not pointed to what parts of the specification provide inherent support for this limitation. Therefore, in the absence of any literal support or explicit explanation as to where inherent support is to be found for the new limitation recited in claim 47, the claim is rejected for comprising impermissible NEW MATTER.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments directed to neural stem cells or progenitor cells obtained from the hippocampus of a rat, does not reasonably provide enablement for embodiments where the neural stem cells or progenitor cells are obtained from any other source. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/12/2004.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is complex in that it involves the introduction of nucleic acids into a particular cell type (i.e. mammalian neural stem or progenitor cells) without the aid of any composition (e.g. soluble receptors, liposomes, etc) or device (e.g. electroporation device) known in the art to aid in such transformation of mammalian cells. The invention is particularly complex in that it apparently involves a "natural" or inherent competency for the recited target cell type that is unexpected and not explained in the instant specification or prior art.

Breadth of the claims: The claims are broad in that they encompass neuronal progenitor or stem cells obtained by any method (e.g. dedifferentiation in culture) obtained from any source (e.g. any source outside of the hippocampus and/or any mammalian source, including humans). This exacerbates the complexity of the invention in that it requires an extrapolation of the data observed in the single experiment described in the instant specification to any type of neuronal

progenitor or stem cell obtained from any mammalian source in any manner, without an underlying basis for one to do so in a predictable manner.

Guidance of the specification/The existence of working examples: The specification describes an experiment in the only working example where plasmid DNAs were transfected into rat progenitor cells isolated from the hippocampus (the sole working example described on pages 11-13). The specification merely demonstrates that the rat neuronal stem or progenitor cells are somehow competent for DNA transfection without the need for treatments usually required for transfection of mammalian cells (e.g. use of a protamine complex or viral carrier to allow receptor-mediated endocytosis). Kidney-derived Cos-7 cells did not exhibit such natural competency for the uptake of exogenous DNAs (e.g. page 12, lines 23-31). No mechanistic explanation is provided as to how these particular neuronal progenitor cells are inherently competent for the uptake of exogenous DNA. The conditions under which the target progenitor cells in this experiment were cultured and the reaction solutions comprising the GFP plasmid are not described in the instant specification. Description of the culture conditions and/or DNA composition might have provided some basis for why these cells are capable of taking up the exogenously added plasmid. Thus, there is simply no basis for the skilled artisan to extrapolate the data presented in the single working example to neuronal progenitor or stem cells obtained from other sources (e.g. other mammalian organisms) in other ways (e.g. from dedifferentiated cells in culture) in a predictable manner.

State of the art/Predictability of the art: The prior art appears to be silent with regard to the natural competency of neuronal stem or progenitor cells for taking up exogenously added nucleic acids. Therefore, the prior art does not offset the deficiencies of the instant specification

with regard to making the claimed methods predictable for neuronal stem or progenitor cells obtained from other sources.

The amount of experimentation necessary: Given that it is known in the art that the isolation of neuronal stem cells or neuronal progenitor cells requires considerable experimentation and that there is no explanation provided by the instant specification or prior art for the observed results described in the sole working example of the instant specification, it would have required undue, unpredictable experimentation of a trial-and-error nature to practice the claimed method in the broad scope currently claimed. Therefore, the instant specification is only found enabling for embodiments wherein the neuronal progenitor or stem cells are isolated from the rat hippocampus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejected claims are directed to methods of introducing a substance comprising a nucleic acid into mammalian neuronal stem or progenitor cells. Each of the claims comprises the limitation of "...wherein the substance gives a detectable signal or encodes a peptide or protein that enables selective identification of the cells, the method comprising (i) bringing the substance into contact with the cell, wherein step (i) is the only prerequisite for the uptake of the substance

by the cell." The term "substance" can reasonably be interpreted as encompassing substances such as liposomes, viral vectors, nucleic acid/chemical compositions, etc., that are known in the art to aid in transformation of target cells. As indicated above, the term "prerequisite" is not explicitly defined in the instant specification and can be interpreted broadly to simply mean that the "substance" is brought into contact with the targeted cells.

Claims 1, 7, 14, 23 & 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al (U.S. Patent No. 6,001,654 A; see the entire patent). **This rejection is maintained for reasons of record in the office action mailed 10/21/2003 and which are repeated below.**

The '654 patent teaches methods for producing a population of mammalian neurons and/or smooth muscle cells comprising contacting at least one mammalian neural stem cell with a culture medium containing one or more growth factors from the TFG-B superfamily (e.g. Abstract; column 3, lines 25-35). The specification teaches that various methods for transforming mammalian cells are known in the art (e.g. DEAE-mediated transfer, calcium phosphate-mediated transfer, viral vectors, etc.; column 7, lines 13-27; column 19, lines 28-column 20, line 32). For example, the patent teaches that neuronal crest stem cells can be transfected via the calcium-phosphate-mediated precipitation/transfection protocol with DNAs encoding an immortalization gene or genes (e.g. v-myc, T antigen, etc.) and/or a cell marker (B-galactosidase) (e.g. column 19, lines 28-column 20, line 32).

Response to Arguments

Applicant's arguments filed 4/21/2004 have been fully considered but they are not persuasive. The response essentially argues that the amendment to the claims obviates the grounds of rejection since the methods of Anderson require known methods/compositions for the transformation of the targeted cells (e.g. DEAE-mediated transfer, calcium-phosphate-mediated precipitation, microinjection, lipofection and viral infection). The response appears to be arguing a limitation that is not actually present in the rejected claims. As indicated above, the amended claims do not actually preclude these methods of introducing nucleic acids into the target neuronal progenitor and stem cells.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

ggl

GERRY LEFFERS
PRIMARY EXAMINER